REMARKS

The Invention.

The present invention provides a composition comprising one or more enzymes non-covalently bound to a peptide backbone, wherein at least one of the enzymes is heterologous to the peptide backbone and the peptide backbone is capable of having bound thereto a plurality of enzymes.

Status of the Application.

Claims 1-29 are pending in the application. Claims 17-29 were withdrawn as directed to a non-elected invention and are cancelled by amendment herein. Claims 1-16 stand rejected. Claims 9 and 10 are cancelled by this amendment. Claims 1 and 16 have been amended to more clearly recite that which the Applicants believe is the invention. The amendment to claim 1 merely incorporates the subject matter of cancelled claim 10 (Figure 6 is the same as SEQ ID NO:29). Claim 13 has been amended to provide adequate antecedent basis. The specification has been amended to address various objections by the Examiner. No new matter is introduced by these amendments.

Information Disclosure Statement

Acknowledgement of Applicants Information Disclosure Statement is noted. Applicants will submit a supplemental IDS to resubmit the Naka reference not initialed upon obtaining a copy thereof.

Objections to the Specification

The Examiner has objected to the specification because Figures 1, 4 and 6 allegedly contain amino acid and/or nucleic acid sequences that do not comply with the sequence rules (see MPEP 2422.02). The rule states

> ...when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, *either* in the drawing *or* in the Brief Description of the Drawings. (Emphasis added.)

First, Applicants note that the description of Figure 1 contains the sequence identifiers for each of the sequences shown in Figure 1. Thus, Figure 1 complied with the rule and has not been amended herein.

Applicants have amended the specification to recite the sequence identifiers for each of the sequences shown in Figures 4 and 6. The description of each of the figures now contains sequence identifiers for each of the sequences shown in the figures.

Withdrawal of the objection is respectfully requested.

35 U.S.C. §112, first paragraph.

Claims 1-7 and 11-16 stand rejected under 35 USC §112, first paragraph as failing to be described in the specification. Specifically, the Examiner asserts that the specification fails to provide any teaching of the structure to function/activity relationship, and that the claims are so broad as to require undue experimentation. Applicants respectfully traverse the rejection.

Applicant asserts that the standard for non-enablement is that the Patent Office must support such assertions with evidence or reasoning substantiating the doubts so expressed. As stated in In re Bowen, 181 U.S.P.Q. 48 (CCPA 1974):

> [T]he only reason given appellant why his specification does not enable one skilled in the art to use his invention as broadly as it is claimed is the statement of the board that "polymerizable materials" include not only . . . all of the very any organic polymers . . . but also inorganic polymers." But even this statement only identifies a subgenus of "polymerizable materials" without giving a reason for the implication inherent therein that inorganic polymers would not work in appellant's process . . .

In the present case, the Office Action provides no extrinsic evidence regarding non-enablement. Instead, the Office Action relies upon the opinion of the Examiner that the breadth of the claim is unsupportable because there aren't enough examples. While the Office Action does review the results provided in the Examples and suggests its position that these results are insufficient, the Office Action is entirely devoid of technical reasoning and/or reference to extrinsic evidence which supports the position therein that one of skill in the art would be unable to make and use the invention as claimed. Accordingly, Applicants respectfully submit that the unsupported opinion of the Examiner

that a specific claimed embodiment is "too broad" is not the standard of non-enablement.

Claims 1-7 and 11-16 stand rejected under 35 USC §112, first paragraph. With regard to structure/function, Applicant has amended claim 1 to recite the presence of the amino acid sequence as shown in SEQ ID NO:29. It has been demonstrated that this sequence is the means for non-covalently binding of the complementary dockerin. See page 7, line 24 et seq. and page 9, line 27 et seq. Applicant has provided that the dockerin and the peptide backbone must be capable of complementary non-covalent binding.

Furthermore, Applicant has provided methods of preparing and using the proteins. See Examples 2 and 3 for dockerins, and Examples 5 and 6 for peptide backbones. In addition, Applicant has provided a method for testing the function of an enzyme, i.e., an assay. See for example, Example 4 demonstrating a lipase assay. Other enzymes would be tested using known assays in a similar manner. This would not involve undue experimentation, but would be routine to one of ordinary skill in the art. Applicant asserts that they have provided written description of their invention and have provided ample exemplification, given the state of the art, to allow one of skill in the art to make and use the invention without undue experimentation. Withdrawal of the rejection is respectfully requested.

35 U.S.C. §112, second paragraph.

Claims 1-16 stand rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, Claim 1 has been rejected for the use of the term "heterologous," Claim 7 has been rejected as failing to teach identifying characteristics of a "derivative of a dockerin derived from *Clostridium* sp.", Claim 13 has been rejected as lacking antecedent basis for the phrase "said internal repeating units", and Claim 16 has been rejected as unclear and having insufficient antecedent basis. Applicants respectfully traverse the rejection.

Claim 1 has been rejected for the use of the term "heterologous" apparently because the Examiner believes that the Applicant has used the word in a way that is

"repugnant to the usual meaning of that term." As the Examiner has noted Applicant has defined the term "heterologous" as "two or more proteins or enzymes which are derived from taxonomically distinct organisms" (see page 7, lines2-5). This is, contrary to the Examiner's assertion, an accepted meaning of the term. The Dictionary of Cell Biology, edited by J. M. Lackie and J. A. T. Dow, in 1995 defined the term "heterologous" as "Of genes or gene products, derived from the tissues or DNA of a different species." Similarly, Webster's II: New College Dictionary, published by Houghton Mifflin Company in 1995 defines "heterologous" as "1. Derived from a different species, as a tissue graft." Applicant will provide a copy of each of these references should the Examiner request. Thus, Applicant's usage of the term "heterologous" is not "repugnant to the usual meaning of that term." Withdrawal of the rejection is respectfully requested.

Claim 7 has been rejected as failing to teach identifying characteristics of a "derivative of a dockerin derived from *Clostridium* sp." Applicant notes that the specification, at page 8, lines 5-14, defines "dockerin" or "dockerin protein", and at page 9, lines 5-11, provides a definition of "derivative". In addition, Applicant has provided the amino acid sequence of a dockerin derived from *Clostridium* sp. in Figure 1. One skilled in the art would be able, from the information presented in the specification, to determine if a sequence is one derived from *Clostridium* sp. or is a derivative thereof. Withdrawal of the rejection is respectfully requested.

Claim 13 has been rejected as lacking antecedent basis for the phrase "said internal repeating units." Applicant has amended Claim 13 to recite the language used in Claim 11 for clarity. Withdrawal of the rejection is respectfully requested.

Claim 16 has been rejected as unclear and having insufficient antecedent basis. Applicant has amended Claim 16 herein for clarity such that it now recites "said peptide backbone with said enzyme." Withdrawal of the rejection is respectfully requested.

35 U.S.C. §102(b).

Claims 1-9 and 11-16 stand rejected under 35 USC §102(b) as being anticipated by Tokatlidis *et al.* (Protein Engineering Vol. 6(8): 947-952 (1993)). Specifically, according to the Office Action:

> Tokatlidis et al. teach the properties conferred on Clostridium thermocellum endoglancase CelC by grafting the duplicated segment of endoglucanse CelD. Specifically, Tokatlidis et al. teach a composition comprising one or more enzymes bound to a peptide backbone, CipA, wherein said enzyme is *heterologous* to said peptide backbone and said backbone is capable of having bound thereto a plurality of enzymes. (Emphasis added.)

Applicant respectfully traverses.

Tokatlidis discloses a fusion protein comprising the duplicated segment of CelD from *Clostridium thermocellum* and the CelC endoglucanase from *C. thermocellum*. Tokatlidis indicate that the fusion protein was expressed as inclusion bodies within the cell in *E. coli* (p. 949). Fractionation of the fusion protein resulted in enzyme activity attributed to the fusion protein (p. 949). Purification of the intact protein from the inclusion bodies by solubilization with 5M urea followed by dialysis also showed that the fusion protein had activity (p. 950). Tokatlidis indicate that the fusion protein bound the CipA scaffolding protein of the cellulosome. With respect to the duplicated segment, Tokatlidis states that it appears that this segment was responsible for inducing inclusion body formation (p. 951). After solubilization of the inclusion bodies in urea, the proteins remained soluble even after removal of the urea (p. 951). Tokatlidis suggests that the altered behavior after salting out indicates that the duplicated segment is prone to participating in hydrophobic interactions.

In fact, Tokatlidis *et al.* merely show that two enzymes from *Clostridium thermocellum* have similar behavior when fused to a duplicating segment and that both enzymes will also bind to the scaffolding protein. This result is not terribly surprising as it was clearly known that the duplicating segment would normally bind to a receptor counterpart on the scaffoldin. As stated in the specification, "[k]nowledge regarding the individual components of the cellulosome and their functional relationships remains limited due to the complex nature of the cellulosome. Importantly, it has not been established that incorporation of heterologous enzyme components into the cellulosome would be successful or that such a heterologous complex could possess enough activity to be functional" (specification, page 5).

Thus, while the disclosure in Tokatlidis is relevant and important, the enzymes selected therein are NOT heterologous, i.e., the fusion protein comprises merely different components already produced by *Clostridium thermocellum*, and the result does not illustrate that active enzyme can be produced. To the contrary, Applicants have explicitly proven that the combination of a dockerin-lipase fusion with the scaffoldin protein from *C. thermocellum* results in a modified "cellulosome" which has lipase activity.

Withdrawal of the rejection is respectfully requested.

35 U.S.C. §103.

Initially, Applicant notes that the test for non-obviousness articulated by the Court of Appeals for the Federal Circuit requires that the combination of the teachings of all or any of the references would have suggested the possibility of further improvement by combining such teachings. Thus, the test of whether it would have been obvious to select specific teachings and combine them must still be met by identification of some suggestion, teaching, or motivation in the prior art, arising from what the prior art would have taught a person of ordinary skill in the field of the invention. *See* In re Dance, 160 F.3d 1339, 48 USPQ2d 1635 *quoting* In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), and In re Vaeck, 20 USPQ2d 1439 (Fed. Cir. 1991).

The Examiner has rejected claims 1-9 and 11-16 as allegedly obvious over the combination of Bayer, *et al.,* Tokatlidis *et al.* and Gerngross *et al.* Applicant respectfully traverses the rejection.

The deficiencies presented above for Tokatlidis *et al.* (under §102) fail to be corrected by Bayer et al. and/or Gerngross *et al.*

The Applicants have amended claim 1, without prejudice and to expedite prosecution, to incorporate the amino acid sequence of the peptide backbone as shown in SEQ ID NO:29. Since neither Bayer, *et al.* nor Tokatlidis, *et al.* disclose or suggest the amino acid sequence of their cellulosomes, the Applicants respectfully suggest neither one of these references, either alone or in combination, renders the claimed invention obvious.

Furthermore, Bayer provides a general disclosure related to the potential for producing "designer cellulosomes" which have different activities and perhaps novel uses in industry. The discussion in Bayer assumes the interchangeability of certain features of the cellulosomes, i.e., the scaffoldin, dockerin and enzymes, in such a manner that heterologous enzymes could be incorporated into the cellulosome. Bayer, however, provides no credible evidence that such heterologous enzymes could or would have been successfully created given the state of the art at the time the application was filed.

Thus, neither Tokatlidis *et al.* nor Bayer *et al.* provide any credible evidence that a scaffolding protein when combined with a heterologous enzyme (as defined in the specification, i.e., derived from taxonomically distinct organism from the scaffolding protein) would result in an active protein.

The reliance on Gerngross *et al.* to correct any other deficiencies is not understood by the Applicant. Gerngross *et al.* teaches the CipA DNA sequence and is not directed to a composition comprising one or more enzymes non-covalently bound to a peptide backbone, wherein at least one of the enzymes is heterologous to the peptide backbone and the peptide backbone is capable of having bound thereto a plurality of enzymes. There is no teaching or suggestion for such a composition.

Withdrawal of the rejection is respectfully requested.

CONCLUSION

In light of the above amendments, as well as the remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7516.

Respectfully submitted,
GENENCOR INTL., INC.

Victoria L. Boyd

Date: October 8, 2003

Victoria L. Boyd
Registration No. 43,510

Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304
Tel: 650-846-7516
Fax: 650-845-6504